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(54) PENETRATION ENHANCERS FOR TRANSDERMAL DELIVERY OF SYSTEMIC AGENTS.

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|---|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|--|--|
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Description

The invention generally relates to an improved method of drug delivery. More particularly, the invention relates to an improved membrane penetration enhancer for use in the transdermal delivery of systemically active drugs to humans and animals.

For some years, pharmaceutical researchers have sought an effective means of introducing drugs into the bloodstream by applying them to unbroken skin. Among other advantages, such administration can provide a comfortable, convenient, and safe way of giving many drugs now taken orally or infused into veins or injected intramuscularly.

Using skin as the portal for drug entry offers unique potential, because transdermal delivery permits close control over drug absorption. For example, it avoids factors that can cause unpredictable absorption from the gastrointestinal tract, including: changes in acidity, motility, and food content. It also avoids initial metabolism of the drug by the liver. Thus, controlled drug entry through skin can achieve a high degree of control over blood concentrations of drug.

Close control over drug concentrations in blood can translate readily into safer and more comfortable treatment. When a drug's adverse effects occur at higher concentrations than its beneficial ones, rate control can maintain the concentrations that evoke only--or principally the drug's desired actions. This ability to lessen undesired drug actions can greatly reduce the toxicity hazards that now restrict or prevent the use of many valuable agents.

Transdermal delivery particularly benefits patients with chronic disease. Many such patients have difficulty following regimens requiring several doses daily of medications that repeatedly cause unpleasant symptoms. They find the same drugs much more acceptable when administered in transdermal systems that require application infrequently--in some cases, only once or twice weekly--and that reduce adverse effects.

Transdermal delivery is feasible for drugs effective in amounts that can pass through the skin area and that are substantially free of localized irritating or allergic effects. While these limitations may exclude some agents, many others remain eligible for transdermal delivery. Moreover, their numbers will expand as pharmaceutical agents of greater potency are developed. Particularly suitable for transdermal delivery are potent drugs with only a narrow spread between their toxic and safe blood concentrations, those having gastrointestinal absorption problems, or those requiring frequent dosing in oral or injectable form.

Transdermal therapy permits much wider use of natural substances such as hormones. Often the survival times of these substances in the body are so short that they would have to be taken many times daily in ordinary dosage forms. Continuous transdermal delivery provides a practical way of giving them, and one that can mimic the body's own patterns of secretion.

At present, controlled transdermal therapy appears feasible for many drugs used for a wide variety of ailments including, but not limited to, circulatory problems, hormone deficiency, respiratory ailments, and pain relief.

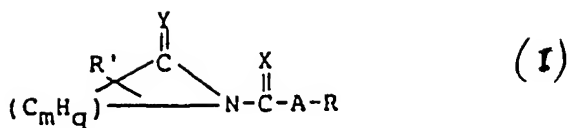
Percutaneous administration can have the advantage of permitting continuous administration of drug to the circulation over a prolonged period of time to obtain a uniform delivery rate and blood level of drug. Commencement and termination of drug therapy are initiated by the application and removal of the dosing devices from the skin. Uncertainties of administration through the gastrointestinal tract and the inconvenience of administration by injection are eliminated. Since a high concentration of drug never enters the body, problems of pulse entry are overcome and metabolic half-life is not a factor of controlling importance.

U.S. Patent Nos. 3,989,815; 3,989,816; 3,991,203; 4,122,170; 4,316,893; 4,415,563; 4,423,040; 4,424,210; and 4,444,762 generally describe a method for enhancing the topical (as contrasted to the systemic) administration of physiologically active agents by combining such an agent with an effective amount of a penetration enhancer and applying the combination topically to humans or animals, in the form of creams, lotions, gels, etc.

Penetration enhancers for enhancing systemic administration of therapeutic agents transdermally are cited in U.S. Patent Nos. 4,405,616; 4,562,075; 4,031,894, 3,996,934; and 3,921,636.

It has been discovered that the penetration enhancers previously disclosed in U.S. Patent Application Serial No. 855,497 to enhance topical delivery of physiologically active agents also enhance the transdermal delivery of systemically active agents through the skin or other body membranes of humans and animals directly into the bloodstream.

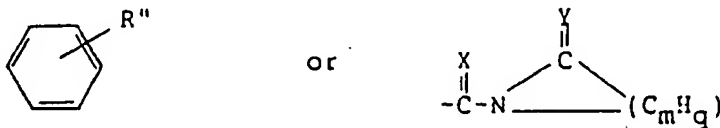
The invention therefore provides a method for manufacturing a composition for the topical administration of systemically active agents through the skin or mucosal membranes of humans and animals in a transdermal device or formulation, said composition comprising an effective amount of a membrane penetration enhancer having the structural formula



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wherein X and Y, each, may represent sulfur, oxygen or two hydrogen atoms, A is a direct linkage or a branched or a straight chain, divalent aliphatic radical having from 0 to 2 double bonds; R' is selected from the group consisting of H, a lower alkyl group having 1-4 carbon atoms, phenyl, lower alkyl or halogen substituted phenyl, acetamido, halogen, piperidiny, lower alkyl or halogen substituted piperidiny, carbal-
 10 koxo, carboxamide, and alkylformyl; m is 3-7; q is 2m-2x wherein x equals the number of double bonds in the azacycloalkene ring and is 1, 2 or 3, and R is CH₃,

15



20 wherein R'' is H or halogen and an effective amount of a physiologically active agent.

Preferably in the above structural formula m R is CH₃, R' is hydrogen, at least one of X or Y is oxygen or sulfur and A is a divalent radical represented by the general formula

25 $-(\text{CH}_2)_n$

25

wherein n is 0 to 17.

In a more preferred embodiment of the present invention Y is oxygen, X represents two hydrogen atoms X is 1 and m equals 5. Even more preferably n is 4 to 16, e.g. 10.

In a further embodiment of the invention, the membrane penetration enhancer is selected from the
 30 group consisting of 1-Dodecylazacyclohept-3-ene-2-one and 1-Dodecylazacyclohept-4-ene-2-one.

Preferably, the systemically active agent is selected from the group consisting of haloperidol, isosorbide dinitrate, nitroglycerin, estradiol, clonidine, propranolol, indomethacine, nifedipine, nicardipine, diclorofenac and metaproterenol.

In still a further embodiment, the above mentioned composition is a gel.

35 The compounds useful as membrane penetration-enhancers in the formulations or devices of the instant invention may be made as described in U.S. Patent Application Serial No. 855,497.

Typical examples of compounds represented by the above structural formula include:

- 1-Methylazacyclohept-4,6-diene-2-one
- 1-Ethylazacyclohept-3-ene-2-one
- 40 3-Methyl-1-(phenylmethyl)-azacyclohept-3-ene-2-one
- 1-Dodecylazacyclohept-3-ene-2-one
- 1-Dodecylazacyclohept-4-ene-2-one
- 1-Dodecylazacyclohept-3,5-dien-2-one
- 1-Methyl-4-phenyl-azacyclohept-4,6,-diene-2-one
- 45 1-Methyl-5-phenyl-azacyclohept-4,6-diene-2-one
- 1-Methyl-6-phenyl-azacyclohept-4,6-diene-2-one
- 4-N,N-Diethylcarbaryl-1-methyl-azacyclohept-4,6-diene-2-one
- 6-N,N-Diethylcarbaryl-1-methyl-azacyclohept-4,6-diene-2-one
- 6-Chloro-1-methyl-azacyclohept-4,6-diene-2-one
- 50 1-Methyl-3-(1-piperidiny)-azacyclohept-3-ene-2-one
- 3-Methoxy-1-methyl-azacyclohept-3-ene-2-one
- 4-Methoxy-1-methyl-azacyclohept-4,6-diene-2-one
- 1-Acetylazacyclohept-3-ene-2-one
- 1-Acetylazacyclohept-4-ene-2-one
- 55 4-Acetyl-1-methyl-azacyclohept-4,6-diene-2-one
- 3-Methyl-1-(phenylmethyl)-azacyclohept-3-ene-2-one

Typical systemically active agents which may be delivered transdermally are therapeutic agents which are sufficiently potent such that they can be delivered through the skin or other membrane to the

bloodstream in sufficient quantities to produce the desired therapeutic effect. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to, anti-infectives, such as antibiotics and antiviral agents, analgesics and analgesic combinations, anorexics, anthelmintics, antiarthritics, antiasthma agents, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antinausea agents, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, including gastrointestinal and urinary; anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations including calcium channel blockers, beta-blockers, antiarrhythmics, antihypertensives, diuretics, vasodilators including general, coronary, peripheral and cerebral; central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, psychostimulants, sedatives and tranquilizers.

Dosage forms for application to the skin or other membranes of humans and animals include creams, lotions, gels, ointments, suppositories, sprays, aerosols, buccal and sub-lingual tablets and any one of a variety of transdermal devices for use in the continuous administration of systemically active drugs by absorption through the skin, oral mucosa or other membranes, see, for example, one or more of U.S. Patents Nos. 3,598,122; 3,598,123; 3,731,683; 3,742,951; 3,814,097; 3,921,636; 3,972,995; 3,993,072; 3,993,073; 3,996,934; 4,031,894; 4,060,084; 4,069,307; 4,201,211; 4,230,105; 4,292,299 and 4,292,303. U.S. Patent No. 4,077,407 and the foregoing patents also disclose a variety of specific systemically active agents which may also be useful in transdermal delivery, which disclosures are hereby incorporated herein by this reference.

Typical inert carriers which may be included in the foregoing dosage forms include conventional formulating materials, such as, for example, water, isopropyl alcohol, gaseous fluorocarbons, ethyl alcohol, polyvinyl pyrrolidone, propylene glycol, fragrances, gel-producing materials such as "Carbopol", stearyl alcohol, stearic acid, spermaceti, sorbitan monooleate, "Polysorbates", "Tweens", sorbital, methylcellulose, etc.

Systemically active agents are used in amounts calculated to achieve and maintain therapeutic blood levels in a human or animal over the Period of time desired. These amounts vary with the potency of each systemically active substance, the amount required for the desired therapeutic or other effect, the rate of elimination or breakdown of the substance by the body once it has entered the bloodstream and the amount of penetration-enhancer in the formulation. In accordance with conventional prudent formulating practices, a dosage near the lower end of the useful range of a particular agent is usually employed initially and the dosage increased or decreased as indicated from the observed response, as in the routine procedure of the physician.

The amount of penetration enhancer which may be used in the invention varies from about 1 to 100 percent although adequate enhancement of penetration is generally found to occur in the range of about 1 to about 10 percent by weight of the formulation to be delivered. The penetration-enhancer disclosed herein may be used in combination with the active agent or may be used separately as a pre-treatment of the skin or other body membrane through which the systemically-active agent is intended to be delivered.

The invention is further illustrated by the following examples which are illustrative of a specific mode of practicing the invention and is not intended as limiting the scope of the appended claims.

EXAMPLE 1

A composition, in the form of a gel, suitable for transdermal delivery of haloperidol, an antidyskinetic or antipsychotic drug, is prepared by mixing the following components in the given concentrations.

Component	Weight %
Haloperidol	1-5
1-Dodecylazacyclohept-3-ene-2-one	1-10
Carbopol 934 P (Available from B.F. Goodrich)	0.5-2
Neutralizing Agent (NaOH)	q.s.
Tween-20 (Available from Atlas Chemical, a Div. of I.C.I.)	1-10
Preservative (Sorbic Acid)	q.s.
Antioxidant (Ascorbic Acid)	q.s.
Chelating Agent (Disodium salt of ethylenediaminetetraacetic acid)	q.s.
Deionized Water	q.s. to 100

This composition is topically applied to the skin of a human subject and after the passage of a suitable period of time haloperidol is found in the bloodstream of said subject.

Example 2

When an amine, e.g. triethylamine or triethanolamine, is substituted for NaOH the results are substantially similar, i.e. a topical composition suitable for transdermally delivering haloperidol to the bloodstream is obtained.

Example 3

When potassium sorbate, or a lower alkyl paraben, e.g. methyl, ethyl, propyl or butyl paraben are substituted for the preservative of the composition of Example 1, the results are substantially similar, i.e. a topical composition suitable for the transdermal delivery of haloperidol to the bloodstream is obtained.

Example 4

When ascorbyl palmitate, Vitamin E, thioglycerol, thioglycolic acid, sodium formaldehyde sulfoxylate, BHA, BHT, propyl gallate or sodium metabisulfite are substituted for the antioxidant of the composition formulated in Example 1, the results are substantially similar in that a topical composition suitable for transdermally delivering haloperidol to the bloodstream is obtained.

Example 5

The composition of Example 1 is prepared in the form of a sodium alginate gel by mixing the following components in the following given concentrations:

Component	Weight %
Haloperidol	1-5
1-Dodecylazacyclohept-3-ene-2-one	1-10
Sodium Alginate	0.5-5
Calcium Salts	q.s.
Tween-20	1-10
Preservative*	q.s.
Antioxidant**	q.s.
Chelating Agent***	q.s.
Deionized Water	to 100

*Suitable preservatives are those used in Example 3 as well as sorbic acid.

**Suitable antioxidants are those used in Example 4 including ascorbic acid.

***The chelating agent is the disodium salt of ethylenediaminetetraacetic acid.

This composition when applied topically is found to transdermally deliver haloperidol to the bloodstream of a subject.

Example 6

The composition of Example 1 is prepared in the form of a hydrophilic cream by mixing the following components.

Component	Weight %
<u>Oil Phase</u>	
Cetyl Alcohol	5-15
Stearyl Alcohol	1-5
1-Dodecylazacyclohept-3-ene-one	0.5-10
Glycerol Monostearate	2-7
<u>Water Phase</u>	
Sodium Laurylsulfate	0.1
Solvent*	2-20
Tween-20	1-5
Water	q.s. to 100

*Suitable solvents are propylene glycol, glycerin, alcohols, for example, ethyl alcohol, isopropyl alcohol, etc. and polyethylene glycols.

The oil phase and the water phase is made up separately, and then agitated to form an emulsion. (When, as in Example 8, the active ingredient, is other than haloperidol, depending on its lipophilicity, it will be distributed in the oil or water phase.) This hydrophilic cream, when applied topically to the skin of a human, is found to transdermally delivery haloperidol into the bloodstream.

Example 7

The composition of the instant invention may also be delivered by use of a polymeric matrix. For example, a solid polymer such as cellulose triacetate, polyvinyl acetate, terpolymers and copolymers of vinyl chloride and vinyl acetate, copolymers of polyvinyl alcohol and polyvinyl acetate, and silicon elastomers is imbibed with a liquid having the following components in the given concentrations.

Component	Weight %
Polymer	5-40
Haloperidol	q.s.
1-Dodecylazacyclohept-3-ene-2-one	0.5-80
Solvent*	5-90
Surfactant**	1-10
Preservative***	q.s.
Antioxidant****	q.s.

*Solvents may be the solvents used in Example 6 above.

**The Surfactant may be Tween-20, glycerol monostearate or sodium laurylsulfate, etc.

***The preservative may be any of the preservatives used in Example 3 above.

****The antioxidants may be any of those used in Example 4 above.

When solid matrix, containing the active ingredients formulated above, is contacted with the skin of a human subject, after a period of time the active agent is found in the bloodstream of said subject.

Example 8

Examples 1 to 7 are repeated except that the following active ingredients in the given concentrations are substituted for haloperidol:

Active Ingredient	Weight %
Isosorbide Dinitrate	5-15
Nitroglycerin	1-5
Estradiol	1-5
Clonidine	0.5-3
Propranolol	1-5
Indomethacine	5-15
Nifedipine	1-5
Nicardipine	1-5
Diclorofenac	5-15
Metaproterenol	1-5

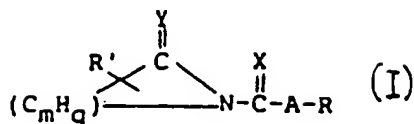
Similar results are obtained in that the active ingredient is transdermally delivered to the bloodstream of an animal.

Example 9

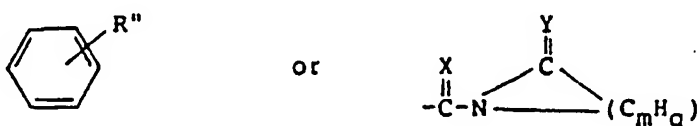
Examples 1 to 8 are repeated except that the compounds exemplified on page 7 (except for 1-Dodecylazacyclohept-3-ene-2-one) are substituted for 1-Dodecylazacyclohept-3-ene-2-one. Similar results are obtained in that the active ingredients are transdermally delivered to the bloodstream of an animal.

Claims

1. A method for manufacturing a composition for the topical administration of systemically active agents through the skin or mucosal membranes of humans and animals in a transdermal device or formulation, said composition comprising an effective amount of a membrane penetration enhancer having the structural formula



wherein X and Y, each, may represent sulfur, oxygen or two hydrogen atoms, A is a direct linkage or a branched or a straight chain, divalent aliphatic radical having from 0 to 2 double bonds; R' is selected from the group consisting of H, a lower alkyl group having 1-4 carbon atoms, phenyl, lower alkyl or halogen substituted phenyl, acetamido, halogen, piperidiny, lower alkyl or halogen substituted piperidiny, carbalkoxy, carboxamide, and alkylformyl; m is 3-7; q is 2m-2x, wherein x equals the number of double bonds in the azacycloalkene ring and is 1, 2 or 3, and R is CH₃,

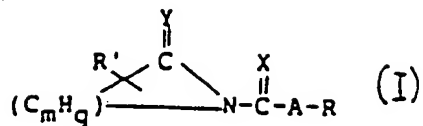


wherein R'' is H or halogen and an effective amount of a physiologically active agent.

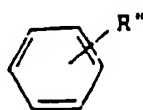
2. The method of claim 1 wherein in the structural formula (I) R' is hydrogen, R is CH₃, at least one of X or Y is oxygen or sulfur and A is a divalent radical represented by the general formula - (CH₂)_n wherein n is 0 to 17.
3. The method of claim 2 wherein in the structural formula (I) X represents 2 hydrogen atoms, Y is oxygen, x is 1 and m is 5.
4. The method of claim 3 wherein in the structural formula (I) n is 4 to 16.
5. The method of claim 4 wherein in the structural formula (I) n is 10.
6. The method of claim 1 wherein the systemically active agent is a therapeutic agent.
7. The method of claim 1 wherein the membrane penetration enhancer is selected from the group consisting of 1-Dodecylazacyclohept-3-ene-2-one and 1-Dodecylazacyclohept-4-ene-2-one.
8. The method of claim 1 wherein the systemically active agent is selected from the group consisting of haloperidol, isosorbide dinitrate, nitroglycerin, estradiol, clonidine, propranolol, indomethacine, nifedipine, nicardipine, diclofenac and metaproterenol.
9. The method of claim 7 wherein the systemically active agent is selected from the group consisting of haloperidol, isosorbide dinitrate, nitroglycerin, estradiol, clonidine, propranolol, indomethacine, nifedipine, nicardipine, diclofenac and metaproterenol.
10. The method of any of Claims 1 to 9 wherein said composition is a gel.

Patentansprüche

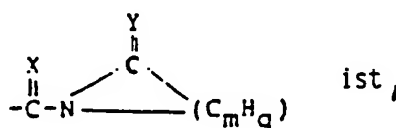
1. Verfahren zur Herstellung einer Zusammensetzung für die topische Verabreichung von systemischen Wirkstoffen durch die Haut oder die Schleimhautmembranen von Menschen und Tieren in einer transdermalen Vorrichtung oder Formulierung, enthaltend eine wirksame Menge einer die Membranpenetration erhöhenden Verbindung mit der Strukturformel



worin X und Y jeweils Schwefel, Sauerstoff oder zwei Wasserstoffatome bedeuten, A eine direkte Bindung oder ein verzweigter oder geradkettiger divalent aliphatischer Rest mit 0 bis 2 Doppelbindungen ist; R' aus der Gruppe bestehend aus H, einer Niedrigalkylgruppe mit 1-4 Kohlenstoffatomen, Phenyl, niedrigalkyl- oder halogensubstituiertem Phenyl, Acetamido, Halogen, Piperidinyl, niedrigalkyl- oder halogensubstituiertem Piperidinyl, Carbalkoxy, Carboxamid und Alkylformyl ausgewählt ist; m 3-7 ist, q 2m-2x ist, worin x der Zahl der Doppelbindungen in dem Azacycloalkenring entspricht und 1, 2 oder 3 ist und R CH₃ ist,



oder

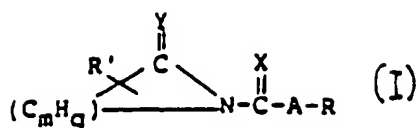


worin R'' H oder Halogen ist und eine wirksame Menge eines physiologisch wirksamen Stoffes.

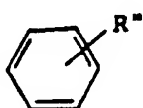
2. Verfahren nach Anspruch 1, bei dem in der Strukturformel (I) R' Wasserstoff, R CH₃, mindestens eines von X oder Y Sauerstoff oder Schwefel ist und A ein zweiwertiger Rest entsprechend der allgemeinen Formel - (CH₂)_n ist, worin n 0 bis 17 ist.
3. Verfahren nach Anspruch 2, bei dem in der Strukturformel (I) X zwei Wasserstoffatome bedeutet, Y Sauerstoff ist und x 1 und m 5 ist.
4. Verfahren nach Anspruch 3, bei dem in der Strukturformel (I) n 4 bis 16 ist.
5. Verfahren nach Anspruch 4, bei dem in der Strukturformel (I) n 10 ist.
6. Verfahren nach Anspruch 1, bei dem der systemische Wirkstoff ein therapeutisches Mittel ist.
7. Verfahren nach Anspruch 1, bei dem der die Membranpenetration erhöhende Verbindung aus der Gruppe bestehend aus 1-Dodecylazacyclohept-3-en-2-on und 1-Dodecylazacyclohept-4-en-2-on ausgewählt ist.
8. Verfahren nach Anspruch 1, bei dem der systemische Wirkstoff aus der Gruppe bestehend aus Haloperidol, Isosorbiddinitrat, Nitroglycerin, Estradiol, Clonidin, Propranolol, Indomethazin, Nifedipin, Nicardipin, Diclofenac und Metaproterenol ausgewählt ist.
9. Verfahren nach Anspruch 7, bei dem der systemische Wirkstoff aus der Gruppe bestehend aus Haloperidol, Isosorbiddinitrat, Nitroglycerin, Estradiol, Clonidin, Propranolol, Indomethazin, Nifedipin, Nicardipin, Diclofenac und Metaproterenol ausgewählt ist.
10. Verfahren nach einem der Ansprüche 1 bis 9, bei dem die Zusammensetzung ein Gel ist.

Revendications

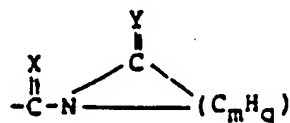
1. Procédé de fabrication d'une composition pour l'administration topique d'agents systématiquement actifs à travers la peau ou les membranes muqueuses de l'être humain et des animaux dans un dispositif ou une formulation transdermique, cette composition comprenant une quantité efficace d'un activateur de pénétration de membrane ayant la formule structurale :



dans laquelle X et Y peuvent représenter chacun du soufre, de l'oxygène ou deux atomes d'hydrogène, A est une liaison directe ou un radical aliphatique bivalent, à chaîne ramifiée ou droite comportant de 0 à 2 doubles liaisons, R' est choisi dans le groupe comprenant H, les groupes alkyle inférieurs comportant 1-4 atomes de carbone, le groupe phényle, les groupes phényle substitués par alkyle inférieur ou halogène, le groupe acétamido, les atomes d'halogène, le groupe pipéridinyle, les groupes pipéridinyle substitués par alkyle inférieur ou halogène et les groupes carbalcoxy, carboxamide et alkylformyle, m est égal à 3-7, q est égal à 2m-2x, où x est égal au nombre de doubles liaisons dans le noyau d'azacycloalcène et vaut 1, 2 ou 3, et R représente un groupe CH₃.



ou



où R'' représente H ou un halogène, et une quantité effective d'un agent physiologiquement actif.

2. Procédé suivant la revendication 1, caractérisé en ce que dans la formule structurale (I) R' représente de l'hydrogène, R représente un groupe CH₃, au moins l'un des X et Y représente de l'oxygène ou du soufre et A est un radical bivalent représenté par la formule générale -(CH₂)_n, dans laquelle n vaut de 0 à 17.
3. Procédé suivant la revendication 2, caractérisé en ce que dans la formule structurale (I) X représente deux atomes d'hydrogène, Y représente de l'oxygène, x est égal à 1 et m est égal à 5.
4. Procédé suivant la revendication 3, caractérisé en ce que dans la formule structurale (I) n vaut de 4 à 16.
5. Procédé suivant la revendication 4, caractérisé en ce que dans la formule structurale (I) n est égal à 10.
6. Procédé suivant la revendication 1, caractérisé en ce que l'agent systématiquement actif est un agent thérapeutique.
7. Procédé suivant la revendication 1, caractérisé en ce que l'activateur de pénétration de membrane est choisi dans le groupe comprenant la 1-dodécylazacyclohept-3-én-2-one et la 1-dodécylazacyclohept-4-én-2-one.
8. Procédé suivant la revendication 1, caractérisé en ce que l'agent systématiquement actif est choisi dans le groupe comprenant l'halopéridol, le dinitrate d'isosorbide, la nitroglycérine, l'oestradiol, la clonidine, le propranolol, l'indométhacine, la nifédipine, la nicardipine, le diclorofénac et le métoprotérénol.
9. Procédé suivant la revendication 7, caractérisé en ce que l'agent systématiquement actif est choisi dans le groupe comprenant l'halopéridol, le dinitrate d'isosorbide, la nitroglycérine, l'oestradiol, la clonidine, le propranolol, l'indométhacine, la nifédipine, la nicardipine, le diclorofénac et le métoprotérénol.
10. Procédé suivant l'une quelconque des revendications 1 à 9, caractérisé en ce que la composition précitée est un gel.